CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

63065/S14, S15

CORRESPONDENCE

ANDA 63-065/S-014, S-015

Danbury Pharmacal, Inc.
Attention: William R. McIntyre, Ph.D.
131 West Street
Danbury, CT 06810

MAR 2 1999

Dear Sir:

Reference is made to your supplemental drug applications dated July 31, 1998, submitted pursuant to 21 CFR 314.70, your abbreviated new drug application for Minocycline Hydrochloride Capsules USP, 100 mg. We note that this product is subject to the exception provisions of Section 125(d)(2) of Title I of the Food and Drug Administration Modernization Act of 1997.

Reference is also made to your amendments dated August 3, and November 5, 1998.

The supplemental applications provide for:

S-014: an additional capsule strength of 75 mg; and

S-015: associated labeling.

The supplemental applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

1. Reference is made to the letter dated November 10, 1999 from the Division of Bioequivalence. We await receipt of your response.

2. Labeling deficiencies:

   a. CONTAINER (100s and 500s)

      i. Increase the prominence of the strength on the container of 100.

      ii. Only six copies of the container were included with this submission.

b. INSERT

Satisfactory in final print. However, only six copies of the insert were included with this submission.

Please revise your labels and labeling as instructed and submit a total of 12 copies of each piece.

The file on these supplemental applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw these supplemental applications. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The responses to this letter will be considered as MAJOR amendments and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving these supplemental applications, you may request an opportunity for a hearing.

Sincerely yours,

Florence Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NOV 10 1998

FILE

ANDA 63-181, Minocycline Hydrochloride Capsules, 50 mg
63-065, Minocycline Hydrochloride Capsules, 100 mg

Danbury Pharmacal, Inc.
Attention: William R. McIntyre, Ph.D.
131 West Street
Danbury, CT 06810

Dear Dr. McIntyre:

This letter is a follow up to our conversation on November 2, 1998, at the Generic Pharmaceutical Industry Technical Workshop in Bethesda, Maryland. As mentioned in our conversation, I had requested that Mr. Don Hare call you regarding a Division of Scientific Investigations (DSI), Office of Compliance audit of the bioequivalence study (8409A) that supported the approval of Danbury's Minocycline HCL capsules. The study was conducted in 1988 at This telephone call was to be made to inform you of the recommendation of the DSI. I subsequently learned from Mr. Hare that in your absence he spoke to Ann Mullarkey on November 2.

In my previous letter dated March 9, 1998, I described the problems that had ensued with your ANDAs for Minocycline HCL capsules due to the bulk drug substance supplied by that was withdrawn from the market due to serious data integrity questions. Since the bulk drug supplied by for your products was withdrawn prior to approval of your application, the data had to be resubmitted. A preliminary evaluation by OGD of the data submitted to support the approval of your drug product utilizing the drug substance manufactured by indicates that it was acceptable. However, an audit of your in vivo bioequivalence study was necessary because it was performed at under the supervision of an individual that had been debarred.

The DSI audit found that the integrity of data generated in Study 8409A is questionable due to the many errors and non-compliant practices involved in the conduct of the study. Therefore, my Office has concluded that the study data are not reliable and do not support the therapeutic equivalence evaluation code determinations for your products. Please refer to page xxi,

paragraph 1.10, "Change of the Therapeutic Equivalence Evaluation for a Single Product" in the 18th Edition of the Orange Book. The procedure that the agency uses to change a therapeutic equivalence evaluation code is outlined in this paragraph.

The following steps are necessary to rectify the situation and prevent the agency from downgrading the therapeutic equivalence evaluation code of Danbury's Minocycline HCL capsules.

(1) Within 60 days of the receipt of this letter, a new bioequivalence study should be initiated.

(2) Ninety days after initiation of the study, ANDA 63-065 should be supplemented with the written report of the new study's results. The Office will expedite the review of Danbury's study results; therefore, you are requested to note "Expedited Review Requested" at the top of your transmittal letter.

(3) If the new bioequivalence study demonstrates that the test and reference drug products are bioequivalent, the therapeutic equivalence evaluation code will not be downgraded. Otherwise, it will be downgraded.

You may continue to market your Minocycline HCL capsules during this interim period, and the agency will refrain from changing the code. However, if you have not responded to this letter within 30 days committing to a new study with the time frames specified, the therapeutic equivalence evaluation code will be downgraded.

If you have any questions regarding this letter, you may contact Mr. Don Hare or Ms. Cecelia Parise of my staff at 301-827-5845.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Danbury Pharmacal, Inc.
131 West Street
Danbury, CT 06810

Tel. 203 744-7200
Fax 203 798-6161

SCHEIN
PHARMACEUTICAL

NEW CORRESP
NC to SCR 014, SL015

April 13, 1999

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Telephone Amendment

Reference: Minocycline Hydrochloride Capsules, USP
(Equivalent to 100 mg Minocycline)
ANDA 63-065 / S-014, S-015

Dear Sir/Madam:

This is in reference to Danbury Pharmacal, Inc.'s (DPI's) approved ANDA 63-065 for Minocycline Hydrochloride Capsules, USP, 100 mg and pending supplement dated July 31, 1998 providing for an additional capsule strength of 75 mg (S-014) and associated labeling (S-015). Reference is also made to a telephone conversation on April 5, 1999 with Ms. Elaine Hu, Office of Generic Drugs, Division of Bioequivalence.

DPI, a wholly owned subsidiary of Schein Pharmaceutical, Inc., is amending the July 31, 1998 supplement to correct a typographical error in the unit amount of Magnesium Stearate, NF indicated for the 75 mg capsule formulation from mg/capsule to mg/capsule. Please note that the quantity of Magnesium Stearate, NF weighed for the 75 mg capsule exhibit batch was correct.

Please replace pp. 44, 53, 184, 202 and 506 of the submission with the enclosed corrected copies. We apologize for any inconvenience this may have caused.

RECEIVED
APR 14 1999
GENERIC DRUGS

We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1) has been provided to the Food and Drug Administration New England District Office in Stoneham, Massachusetts.

Included in this submission is an extra copy of our cover letter. Please acknowledge by date stamping this letter upon receipt and forwarding this copy to us in the self-addressed stamped envelope provided for your convenience.

Please contact the undersigned at (914) 278-3735 or by fax at (914) 278-3741 if you have any questions regarding this submission.

Sincerely,

Ann Mullarkey

Ann Mullarkey
Director
Regulatory and Professional Affairs

cc: Mr. Mark Anderson, Project Manager, Office of Generic Drugs (fax copy, cover letter only)
Ms. Brenda Holman, District Director, Buffalo Office
Mr. Jeremiah Beckwith, Acting District Director, San Juan District Office

Danbury Pharmacal, Inc.
131 West Street
Danbury, CT 06810

Tel. 203 744-7200
Fax 203 798-6161

SCHEIN
PHARMACEUTICAL

April 5, 1999

NDA SUPP AMEND
SCQ 014 / AC
SL 015 / AL

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Minor Amendment

Reference: Minocycline Hydrochloride Capsules, USP
(Equivalent to 100 mg Minocycline)
ANDA 63-065 / S-014, S-015

Dear Sir/Madam:

This is in reference to Danbury Pharmacal, Inc.'s (DPI) approved ANDA 63-065 for Minocycline Hydrochloride Capsules, USP, 100 mg and pending supplement dated July 31, 1998 providing for an additional capsule strength of 75 mg (S-014) and associated labeling (S-015). Reference is also made to your correspondence dated March 2, 1999 and a telephone conversation on March 15, 1999 between Mr. Mark Anderson, Office of Generic Drugs, and Mr. Robert Pollock, Lachman Consultant Services, Inc. on DPI's behalf.

DPI, a wholly owned subsidiary of Schein Pharmaceutical, Inc., is providing the following information in response to the Agency's March 2, 1999 letter:

Comment 1: Reference is made to the letter dated November 10, 1998 from the Division of Bioequivalence. We await receipt of your response.

Response: On March 3, 1999, DPI submitted the final study report and the *in vitro* dissolution data for DPI's Minocycline Hydrochloride Capsules, USP, 100 mg and Lederle Laboratories's MINOCIN® (minocycline hydrochloride) Capsules, 100 mg used in the *in vivo* bioavailability/bioequivalence study for Minocycline Hydrochloride Capsules, USP. An expedited review was requested in accordance with the Agency's November 10, 1998 correspondence.

RECEIVED
APR 6 1999
GENERIC DRUGS

Comment 2: Labeling Deficiencies:

Enclosed as Exhibit I are 12 copies of the final printed insert. The container labels for the 100s and 500s sizes have been revised in accordance with your comment in the March 2, 1999 correspondence. Please see Exhibit II for 12 copies of the 100s and 500s final printed container labels.

As discussed with Mr. Anderson on March 15, 1999, DPI is requesting reconsideration of the classification of this amendment. We believe that based on the absence of chemistry issues and the minor nature of the labeling revisions in the Agency's March 2, 1999 letter, along with the expedited review of our pending bioequivalence supplement, this amendment should be considered as minor.

Included in this submission is an extra copy of our cover letter. Please acknowledge by date stamping this letter upon receipt and forwarding this copy to us in the self-addressed stamped envelope provided for your convenience.

Please contact the undersigned at (914) 278-3735 or by fax at (914) 278-3741 if you have any questions regarding this submission.

Sincerely,

Ann Mullarkey
Director
Regulatory and Professional Affairs

cc: Mr. Mark Anderson, Project Manager, Office of Generic Drugs (fax copy, cover letter only)

Danbury Pharmacal, Inc.
131 West Street
Danbury, CT 06810

Tel. 203 744-7200
Fax 203 798-6161

SCHEIN
PHARMACEUTICAL

November 5, 1998

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA SUPPL AMENDMENT
SCA-014
AC

Amendment

Reference: Minocycline Hydrochloride Capsules, USP
(Equivalent to 100 mg Minocycline)
ANDA 63-065

Dear Sir/Madam:

Please refer to Danbury Pharmacal, Inc.'s (DPI) supplement dated July 31, 1998 to our approved ANDA 63-065 for Minocycline Hydrochloride Capsules, USP, 100 mg. The July 31, 1998 supplement provided for an additional capsule dosage strength, Minocycline Hydrochloride Capsules, USP, 75 mg.

Danbury Pharmacal, a wholly owned subsidiary of Schein Pharmaceutical, Inc., is hereby amending Section IV: Bioavailability/Bioequivalence in our July 31, 1998 supplement to include additional *in vitro* dissolution data. DPI is submitting *in vitro* dissolution profile data for two lots of the reference listed drug, Lederle Laboratories' MINOCIN® (minocycline hydrochloride) Capsules, USP, 100 mg. The dissolution data for MINOCIN® Lot 168-494 was submitted with our original application and was used as the comparator lot in our 1988 biostudy for Minocycline Hydrochloride Capsules, USP, 100 mg. We are also submitting for the first time dissolution data for a recently manufactured lot of MINOCIN® (minocycline hydrochloride) Capsules, 100 mg, Lot 456-225.

We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1) of this submission has been provided to the Food and Drug Administration New England District Office in Stoneham, Massachusetts.

RECEIVED
NOV 06 1998
GENERIC DRUGS

Included in this submission is an extra copy of our cover letter. Please acknowledge by date stamping this letter upon receipt and forwarding this copy to us in the self-addressed stamped envelope provided for your convenience.

Please contact the undersigned at (914) 278-3742 or by fax at (914) 278-3741 if you have any questions regarding this submission.

Sincerely,

Valerie Daly for

William R. McIntyre, Ph.D.
Vice President
Regulatory Affairs
Schein Pharmaceutical, Inc.

cc: Ms. Brenda Holman, District Director, Buffalo Office
Mr. Samuel Jones, District Director, San Juan District Office

Danbury Pharmacal, Inc.
131 West Street
Danbury, CT 06810

Tel. 203 744-7200
Fax 203 798-6161

SCHEIN
PHARMACEUTICAL

August 3, 1998

NEW CORRESP
(5-14, 15)

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Noted: note placed = 7/31 pkg + chem rt
Mark Anderson
8/7/98

Reference: Minocycline Hydrochloride Capsules, USP
(Equivalent to 100 mg Minocycline)
ANDA 63-065

Dear Sir/Madam:

Danbury Pharmacal, Inc. is resubmitting the cover letter to the July 31, 1998 supplement to Minocycline Hydrochloride Capsules, USP, 100 mg ANDA 63-065 for an additional dosage strength of 75 mg. There was an error in the original cover letter dated July 31, 1998. Please include the enclosed August 3, 1998 cover letter with the July 31, 1998 supplement. We apologize for any inconvenience.

Please contact the undersigned at (914) 278-3742 or by fax at (914) 278-3741 if you have any questions regarding this submission.

Sincerely,

William R. McIntyre, Ph.D.
Vice President
Regulatory and Professional Affairs

RECEIVED
AUG 0 4 1998
GENERIC DRUGS

cc: Ms. Brenda Holman, District Director, Buffalo Office
Mr. Samuel Jones, District Director, San Juan District Office
Mr. John Marzilli, District Director, New England District Office

8.1.98

NDA NO. _____ REF NO. SCQ014
NDA SUPPL FOR New Strength

NDA NO. _____ REF NO. SL015
NDA SUPPL FOR Label ext

Danbury Pharmacal, Inc.
131 West Street
Danbury, CT 06810
Tel. 203 744-7200
Fax 203 798-6161

BIOAVAILABILITY
Opt's BIO

SCHEIN PHARMACEUTICAL

Noted
Appears appropriate
review assignments
have been made
/s/ Anderson
8/4/98

July 31, 1998

Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Supplement for an
Additional Dosage Strength

Labeling complete
Not reviewed
R. Hatcher
9/23/97

Reference: Minocycline Hydrochloride Capsules, USP
(Equivalent to 100 mg Minocycline)
ANDA 63-065

Dear Sir/Madam:

Please refer to Danbury Pharmacal, Inc.'s (DPI) approved ANDA 63-065 for Minocycline Hydrochloride Capsules, USP (Equivalent to 100 mg Minocycline) and ANDA 63-181 for Minocycline Hydrochloride Capsules, USP (Equivalent to 50 mg Minocycline).

On January 23, 1998, Lachman Consultant Services, Inc. submitted a suitability petition under Section 505 (j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (Act) requesting permission to submit an ANDA for Minocycline Hydrochloride Capsules, USP, (Equivalent to 75 mg Minocycline). This petition, filed as Docket No. 98P-0042/CP1, was approved by the Agency on May 26, 1998. A copy of the Agency's letter approving the petition allowing for a 75 mg capsule is included in Section II.

Danbury Pharmacal, Inc., a wholly owned subsidiary of Schein Pharmaceutical, Inc., is hereby submitting a supplement to the approved ANDA 63-065 for the addition of an additional dosage strength, Minocycline Hydrochloride Capsules, USP, (Equivalent to 75 mg Minocycline). Minocycline Hydrochloride Capsules, USP, 75 mg will be labeled using distributor labeling for Medicis, The Dermatology Company®. DPI currently distributes Minocycline Hydrochloride Capsules, 50 mg and 100 mg under the approved Medicis labeling in addition to the approved Schein labeling.

RECEIVED
AUG 0 3 1998
GENERIC DRUGS

8/11 ok

The route of administration, dosage form, active ingredient and labeling (except for minor editorial changes and the inclusion of the 75 mg strength) for Medicis Minocycline Hydrochloride Capsules, USP, 75 mg are the same as those approved for Medicis Minocycline Hydrochloride Capsules, 100 mg. Additionally, we are submitting an annotated side by side comparison to the innovator's labeling. As previously stated, the different strength of the 75 mg capsules from the listed drug product has been submitted in an approved petition.

The bioavailability/bioequivalence study was conducted in 1988 on Danbury Pharmacal's Minocycline Hydrochloride Capsules, USP (Equivalent to 100 mg Minocycline) and Lederle Laboratories's MINOCIN® (minocycline hydrochloride) Capsules, 100 mg. DPI's formulation for Minocycline Hydrochloride Capsules has not changed since that time. The *in-vitro* dissolution profile for Minocycline Hydrochloride Capsules, USP, 75 mg is comparable to the profiles for the ANDA biobatch and a recent production batch for Minocycline Hydrochloride Capsules, USP, 100 mg and MINOCIN® Capsules, 100 mg. Since the formulations of DPI's Minocycline Hydrochloride Capsules, 75 mg and 100 mg are dose proportional, a "common blend" will be utilized to encapsulate either the 75 mg or 100 mg capsules.

Danbury Pharmacal is submitting a request for a waiver for the bioavailability/bioequivalence study for Minocycline Hydrochloride Capsules, USP, 75 mg. Per the Food and Drug Administration Modernization Act of 1997, the approval of DPI's Minocycline Hydrochloride Capsules ANDAs prior to November 20, 1997 exempts this application from the patent and exclusivity provisions in section 505.

Danbury Pharmacal will be manufacturing and testing Minocycline Hydrochloride Capsules, USP, 75 mg at its alternate site in . site is an approved alternate facility for the manufacture of Minocycline Hydrochloride Capsules, USP, 100 mg. A two year expiration date is requested and is supported by one, two and three months accelerated stability data (40°C/75% relative humidity) in the container/closure sizes intended for marketing. The composition and specifications of the container/closure system are identical to the container/closure system approved for ANDA 63-065 except for the bottle and cap sizes which are intermediate to the sizes approved for the 100 mg capsules.

Following this letter is a table of contents to facilitate the review of this supplemental application.

We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1) of this submission has been provided to the Food and Drug Administration New England District Office in Stoneham, Massachusetts.

Included in this submission is an extra copy of our cover letter. Please acknowledge by date stamping this letter upon receipt and forwarding this copy to us in the self-addressed stamped envelope provided for your convenience.

Please contact the undersigned at (914) 278-3742 or by fax at (914) 278-3741 if you have any questions regarding this submission.

Sincerely,

William R. McIntyre, Ph.D.
Vice President
Regulatory and Professional Affairs

cc: Ms. Brenda Holman, District Director, Buffalo Office
Mr. Samuel Jones, District Director, San Juan District Office